

Serial No. 09/745,226

REMARKS

Status of the Claims

Claims 33-48, 50-56 and 58-70 are presently pending. Claims 50, 52, 53 and 54 are amended.

Response to Office Action

1. Rejection of Claims 50-54, 35 USC §112, first paragraph

Claims 50-54 are rejected under 35 USC §112, first paragraph, because the Office Action contends that the specification, although being enabling for treating the various disorders claimed, does not provide sufficient enablement for prevention. Applicants respectfully traverse this rejection and its supporting remarks.

Moreover, claims 50, 52, 53 and 54 have been amended to recite "A method of treating a condition selected from. . ." Therefore it is respectfully submitted that the outstanding rejection under 35 USC §112, first paragraph is now moot with respect to these claims.

Claim 51 continues to be directed to a method of treating or preventing restenosis in a patient using the drug delivery system of claim 33. It is respectfully submitted, however, that nitric oxide is known for both treatment *and* prevention restenosis. See, e.g., U.S. Patent No. 5,770,645 to Stamler et al. at col. 1, lines 22-30. See also *Id.* at col. 9, line 59 to col. 10, line 4. Thus, it is believed that claim 51 is fully in compliance with the provisions of 35 USC §112, first paragraph.

In view of the above reconsideration and withdrawal of the outstanding rejection of claims 50-54 under 35 USC §112, first paragraph, are therefore respectfully requested.

2. Rejection of Claims 33-48, 50-52, 56 and 58-70 under 35 USC §103(a)

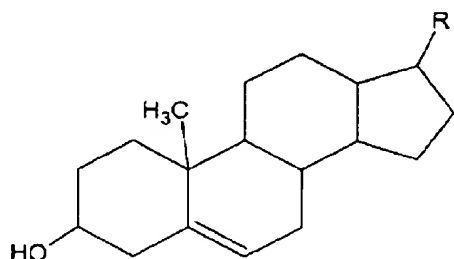
Claims 33-48, 50-52, 56 and 58-70 are rejected under 35 USC §103(a) over U.S. Patent No. 5,770,645 ("Stamler") in view of U.S. Patent No. 5,698,738 ("Garfield"). The Applicants respectfully traverse this rejection and its supporting remarks.

In order to establish a *prima facie* case of obviousness under 35 U.S.C. §103, (a) there must be some suggestion or motivation to modify/combine the references of record, and (b) there must be a reasonable expectation of success. See MPEP §2143. The

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teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *Id.* The mere fact that references *can* be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination or modification. MPEP 2143.01 (emphasis added) (citing *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990)).

Claim 33, the only independent claim presently pending, is directed to a drug delivery system comprising a medical article and a nitric oxide releasing compound comprising a lipid molecule selected from (a) phosphoglycerides, (b) lipid molecules having a sphingosine base as a backbone, (c) monoacylglycerols, (d) diacylglycerols, (e) glycosylacylglycerols, and (f) sterol molecules of the formula:



where R is a branched aliphatic chain of eight or more carbon atoms, wherein the lipid molecule further comprises a nitric-oxide containing group selected from (a) a

—S—N=O group, (b) a —O—N=O group, and (c) a >N—N=O group.

With respect to Stamler, the Office Action points to the portion of Stamler at col. 3, lines 55-58, where it is stated that “[p]olymers can be hydrophilic, amphiphilic or hydrophobic,” presumably as evidence that Stamler teaches the use of hydrophobic NO-delivering species.

Upon close examination, however, it becomes clear that the above statement from Stamler really says nothing about the hydrophilic/hydrophobic characteristics that the NO-delivering species should possess, because it covers essentially all the possibilities: hydrophilic, hydrophobic, or both (amphiphilic).

The paragraph that follows the above statement (see col. 3, lines 59 *et seq.*), on the other hand, does make clear Stamler's preference, which is for NO-delivering species that are hydrophilic in nature.

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Moreover, in contrast to the present invention, Stamler teaches the use of *polymers* as NO-delivering species. According to Stamler, this allows NO-delivering species to be used, for example, as a coating for a medical device, which coating also delivers nitric oxide *in vivo* to a treatment site. See Stamler Abstract.

Thus, Stamler teaches the use of an NO-delivering entity that is (a) hydrophilic and (b) polymeric. The NO- bearing species of the invention as claimed in claim 33, on the other hand, are neither hydrophilic (they are lipids and hence lipophilic) nor polymeric.

The Office Action concedes that Stamler does not teach the use of lipids in medical articles as NO-releasing molecules, but nonetheless concludes that this deficiency addressed by the teachings of Garfield. The applicants respectfully disagree. For example, with regard to Garfield, the Office Action states that:

Garfield teaches that suitable pharmaceutically acceptable carriers include vegetable oils, polyethylene glycol, and hydroxypropyl methylcellulose and that fats (vegetable oils) may be used as carriers utilizing microencapsulation....These properties of fats render obvious the use of lipids in combination with NO.

However, while Garfield teaches that oils can be provided in addition to the NO-delivering species, either as carriers or microencapsulants, this does not provide motivation to add oil to the NO-delivering compositions of Stamler. For example, as noted above, the NO-delivering species in Stamler are polymers, which can be used as coatings for medical devices. As a result, there is no need for a carrier or a microencapsulant for the NO-delivering species in Stamler's devices.

Furthermore, even assuming *arguendo* that oil is added to the NO-delivering compositions of Stamler, such an addition would still not lead to the invention as claimed in claim 33. In this connection, please note that Garfield teaches *the addition of* oils as carriers or microencapsulants for the NO-delivering species. In the claimed invention, on the other hand, the lipids and the NO-delivering species are not separate entities; rather they are one and the same.

The Office Action further points to the disclosure, in Garfield, of a steroid compound having an attached NONOate anion. In contrast, and as noted above, Stamler teaches the use of NO-delivering *hydrophilic polymers* as medical device coatings.

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Because the steroid NONOates of Garfield are neither *polymers* nor *hydrophilic*, it is respectfully submitted that one of ordinary skill in the art would not have been motivated to incorporate these species into the devices of Stamler, absent hindsight afforded by the present application.

The Office Action further argues that "[o]ne would be motivated to use lipids as the R group [of the NONOate anion of Garfield] because lipids are known to form liposomes, wherein an additional active agent could be entrapped in the liposome which would then provide an additional therapeutic activity." This, however, is not the case.

First, it is respectfully submitted that there is no teaching or suggestion to utilize liposomes in the device of Stamler. Indeed, there does not appear to be any discussion whatsoever concerning the use of liposomes in either Stamler or Garfield. It is admitted that liposomes are discussed in the present specification (see page 4, line 20, and claim 41), but applicants' own disclosure cannot be used to reject the claims of the present invention, either explicitly as a reference, or implicitly as a blueprint to perform a hindsight reconstruct of the present invention.

Moreover, even assuming *arguendo* that one of ordinary skill in the art would have been motivated to create a liposome as alleged in the Office Action, it is respectfully submitted that that person would have utilized commercially available and recommended species for liposome formation, rather than resorting to the steroidal NONOates of Garfield. In this connection, it is noted that the Office Action has provided no evidence that simply selecting a steroid molecule as the R group in Garfield would inherently provide the lipid bilayer membrane that is characteristic of liposomes. (Note that liposomes are commonly constructed using phospholipids.)

For at least the above reasons, it is respectfully submitted that claim 33 is patentable over Stamler in view of Garfield under 35 U.S.C. 103(a).

At least because they are dependent upon claim 33, claims 34-48, 50-52, 56 and 58-70 are likewise patentable over Stamler in view of Garfield.

Accordingly, reconsideration and withdrawal of the rejection of claims 33-48, 50-52, 56 and 58-70 under 35 U.S.C. 103(a) as being unpatentable over Stamler in view of Garfield are respectfully requested.

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3. Rejection of Claims 33-48, 50-54, 56 and 58-70 under 35 USC §103(a)

Claims 33-48, 50-54, 56 and 58-70 are rejected under 35 USC §103(a) over Stamler in view of Garfield as applied above and further in view of U.S. Patent No. 5,814,666 ("Green"). The Applicants respectfully traverse this rejection and its supporting remarks.

As noted above, independent claim 33 is presently patentable over Stamler in view of Garfield. Green, which cited as teaching the treatment of diseases using nitric oxide, does not make up for the above-noted deficiencies in Stamler and Garfield.

For at least this reason, it is respectfully submitted that claim 33 is patentable over Stamler in view of Garfield and further in view of Green under 35 U.S.C. 103(a).

At least because they are dependent upon claim 33, claims 34-48, 50-54, 56 and 58-70 are likewise patentable over Stamler in view of Garfield and further in view of Green.

Accordingly, reconsideration and withdrawal of the rejection of claims 33-48, 50-54, 56 and 58-70 under 35 U.S.C. 103(a) are respectfully requested.

4. Rejection of Claims 33-48, 50-52, 55, 56 and 58-70 under 35 USC §103(a)

Claims 33-48, 50-52, 55, 56 and 58-70 are rejected under 35 USC §103(a) over Stamler in view of Garfield as applied above and further in view of U.S. Patent No. 5,519,020("Smith"). The Applicants respectfully traverse this rejection and its supporting remarks.

As noted above, independent claim 33 is presently patentable over Stamler in view of Garfield. Smith, which is cited for its teaching of wound healing using NONOate complexes, does not make up for the above-noted deficiencies in Stamler and Garfield.

For at least this reason, it is respectfully submitted that claim 33 is patentable over Stamler in view of Garfield and further in view of Smith under 35 U.S.C. 103(a).

At least because they are dependent upon claim 33, claims 34-48, 50-52, 55, 56 and 58-70 are likewise patentable over Stamler in view of Garfield and further in view of Smith.

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Accordingly, reconsideration and withdrawal of the rejection of claims 33-48, 50-52, 55, 56 and 58-70 under 35 U.S.C. 103(a) are respectfully requested.

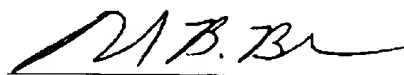
CONCLUSION

Applicants submit that the claims of the present invention are in condition for allowance, early notification of which is earnestly solicited. Should the Examiner be of the view that an interview would expedite consideration of this Amendment or of the application at large, request is made that the Examiner telephone the Applicant's attorney at (703) 433-0510 to resolve any outstanding issues.

FEES

The Office is authorized any required fees to deposit account number 50-1047.

Respectfully submitted,



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